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Structural study of 3-methyl-3-azabicyclo[3.3.1]nonan-9-ols functionalized at the 1-position by molecular mechanics calculations and NMR spectroscopy

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ABSTRACT: The α and β epimers of 1-hydroxymethyl-3-methyl-3-azabicyclo[3.3.1]nonan-9-ol (**1** and **2**) and ethyl 9-hydroxy-3-methyl-3-azabicyclo[3.3.1]nonane-1-carboxylate (**3** and **4**) were studied by molecular mechanics and ^{1}H and ^{13}C NMR spectroscopy. These compounds always prefer a slightly flattened chair–chair (CC) conformation with the *N*-CH_3 group in the equatorial position. It can be assumed that the bicyclic system exists as a single conformation except for diol **2** in non-polar solvents, where the contribution of the N···H—O bonded BC form is estimated to be around 39%. Theoretical calculations provide reasonably good support for the observed conformational preferences of the hydroxymethyl and ethoxycarbonyl groups. Copyright © 2000 John Wiley & Sons, Ltd.

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KEYWORDS: azabicyclic compounds; conformation; molecular mechanics; NMR

INTRODUCTION

Extensive structural studies on substituted bicyclo[3.3.1]-nonanes and hetero analogs have been reported because of the presence of this framework in a large number of natural and synthetic bioactive compounds.[1–3] In connection with our interest in the preparation, structural and pharmacological studies of 3-azabicyclo[3.3.1]nonane derivatives,[4–6] we present in this paper a structural study of the α and β epimers of 1-hydroxymethyl-3-methyl-3-azabicyclo[3.3.1]nonan-9-ol (**1** and **2**) and ethyl 9-hydroxy-3-methyl-3-azabicyclo[3.3.1]nonane-1-carboxylate (**3** and **4**) (Scheme 1) performed by molecular mechanics (MM) calculations and NMR spectroscopy. This azabicyclic system is structurally related to the 9- and 1-azabicyclo[3.3.1]nonane skeletons, present in granisetron and renzapride, potent 5-HT_3 receptor antagonists,[3] and some derivatives have been shown to be HIV protease inhibitors useful for the treatment of AIDS.[7] As several of the structure–activity relationships developed for bioactive compounds have been rationalized in terms of the ability of the low-energy conformations to fit optimally all the requirements of the pharmacophore models,[8] we have focused on the role of the ethoxycarbonyl and hydroxymethyl groups at the 1-position. Accumulating evidence suggests that the conformational properties of the 3-azabicyclo[3.3.1] nonane derivatives are governed mainly by steric factors,[1,2,4–6,9] and the MM method[2,6] and *ab initio* calculations[2,9] have proven useful in predicting their structural features. The conformational preferences of these compounds were compared with those previously reported for α and β 3-methyl-3-azabicyclo[3.3.1]nonan-9-ol (**5** and **6**) and ethyl 3-methyl-9-oxo-3-azabicyclo [3.3.1]nonane-1-carboxylate (**7**).[5,6]

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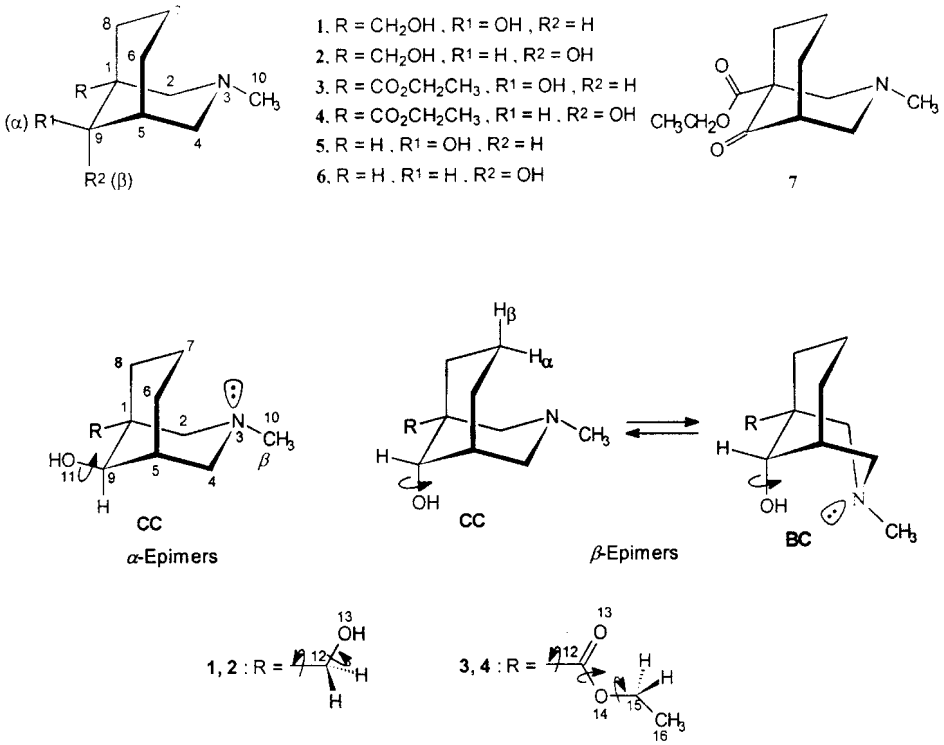
RESULTS AND DISCUSSION

MM calculations

For the bicyclic system, eight possible conformations must be envisaged owing to its potential flexibility and the two spatial orientations of the *N*-group on the piperidine ring (3α or *endo* and 3β or *exo*[2,6]) by nitrogen inversion. However, experimental and theoretical data indicate that 9-substituents and/or the presence of a heteroatom at the 3-position increase the preference for the chair–chair conformation, with the relative orientation of the 3-substituent practically fixed in the *exo* (equatorial) position.[1,2,4–6,9] The



Scheme 1

alternative forms in which the six-membered rings adopt a boat or twist-boat conformation become so energetically unfavourable that their participation in the conformational equilibrium is negligible unless stabilizing through-space interactions, such as intramolecular hydrogen bonds, can make an effective contribution.[1,2,6,10] According to these findings, the α-epimers, **1** and **3**, may be restricted to the chair–chair form, with the *N*-CH_3 group in the equatorial position (CC, Scheme 1). However, in the case of the β epimers, **2** and **4**, the two conformations represented in Scheme 1 were chosen since the form in which the piperidine ring adopts a boat or twist-boat conformation with an *endo* orientation of the *N*-CH_3 group (BC) could be stabilized by intramolecular N···H—O bonding. The conformational preferences of the hydroxy, hydroxymethyl and ethoxycarbonyl groups were explored for each conformation of the bicyclic system using the MMX force field[11,12] [PC-MODEL 386(92) program (Serena Software, Bloomington, IN, USA)]. Calculations were performed with and without consideration of hydrogen bonding to explain the solvent dependence of the conformational changes observed in solution.

Disregarding H-bonding, the MM calculations indicate a CC conformation of the bicyclic system, the BC form of the β epimers is strongly destabilized and a high flexibility of the substituents. For diols **1** and **2**, the three staggered forms of the hydroxymethyl group, by rotation around the C1—C12 bond, make a significant contribution. These forms are characterized by the torsion angle C2—C1—C12—O13 and are denoted as **a**, **b** and **c** (180, −60 and 60°, respectively). Thus, for **1**, the **c** form, with an *anti* orientation of the OH group (O13-H) with respect to C8, should amount to about 58% of the conformational mixture at room temperature, followed by the **b** arrangement (24%). The **a** conformation is the most unfavourable (18%), because of the 1,3-parallel relative orientation of the two OH groups. A similar trend was found for diol **2**: the **a** form is preferred (60%), while the low stability corresponds to the **c** orientation (17%). The calculated preference is always for an *anti* arrangement of the O13—H bond with respect to C1 and a *gauche* orientation with respect to H-9 for the O11—H bond.

For hydroxy esters **3** and **4** the conformational preferences of the ethoxycarbonyl and hydroxy groups were checked by rotation around the C1—C12, C12—O14, O14—C15 and C9—O11 bonds (Scheme 1). According to MM calculations, the conformation of the C12—O14 system is practically fixed, with a value of the torsion angle C1—C12—O14—C15 of about 180°. Additionally, the energy content of the three staggered conformations around the O14—C15 bond is very similar, with the *anti* orientation of the methyl group with respect to C12 slightly favoured. A similar trend was found for the keto ester **7** on the basis of NMR data and MM calculations.[5,6] However, some differences arise for the C1—C12 fragment. This system can adopt two spatial arrangements: **a**, in which the carbonyl group is almost eclipsed with the bicyclic carbon C9, and **b**, where they are practically in an *anti* orientation, with a clear

Table 1. Relative energies (kcal mol^{-1}), populations and significant torsion angles (degrees) for the selected conformations of diols **1** and **2** and hydroxy esters **3** and **4** computed with the contribution of hydrogen bonds[a]

	1, CC					
	a-1[b]	**a-2**[b]	**a-3**[c]	**a-4**[c]	**b**	**c**
C2C1C12O13	175	173	179	177	−60	68
HO13C12C1	−168	77	−39	−52	−176	−173
HO11C9H9	−77	−68	43	174	60	−41
Energy	0.45	0.00	0.81	1.01	4.25	3.18
N_i	0.25	0.52	0.13	0.10	—	—

	2, CC						
	a	**b**	**c-1**[c]	**c-2**[b]	**c-3**[b]	**c-4**[c]	**2**, BC, **c**[d]
C2C1C12O13	170	−64	57	61	61	59	59
HO13C12C1	175	178	41	169	−76	58	54
HO11C9H9	42	−58	−39	77	69	−174	−177
Energy	2.82	4.01	0.46	0.16	0.00	1.41	2.35
N_i	—	—	0.20	0.32	0.43	0.04	0.02

	3, CC					
	a-1[b]	**a-2**	**a-3**	**b-1**	**b-2**	**b-3**
C8C1C12O13	−100	−175	−179	58	41	12
C9C1C12O13	19	−55	−58	179	162	140
HO11C9H9	−53	47	170	−32	45	171
Energy	0.00	1.61	3.48	1.50	2.24	3.36
N_i	0.85	0.06	—	0.07	0.02	—

	4, CC						
	a-1[b]	**a-2**	**a-3**	**b-1**	**b-2**	**b-3**	**4**, BC[e]
C8C1C12O13	−128	−68	−55	74	93	105	80
C9C1C12O13	−11	48	61	−167	−148	−137	−162
HO11C9H9	50	−39	−165	28	−43	−167	−172
Energy	0.00	1.52	4.20	1.45	2.03	4.17	5.66
N_i	0.83	0.07	—	0.07	0.03	—	—

[a] Values obtained for $\varepsilon = 1.0$; an increase of ε reduces the contribution of this stabilizing factor.
[b] d(O13···HO11) = 1.80 (**1**,**a-1** and **2**,**c-3**), 1.81 (**1**,**a-2**), 1.79 (**2**,**c-2**), 1.97 (**3**,**a-1**) and 1.99 Å (**4**,**a-1**).
[c] d(O11···HO13) = 1.79 Å (**1**,**a-3** and **2**,**c-1**) and 1.82 Å (**1**,**a-4** and **2**,**c-4**).
[d] d(N3···HO11) = 1.90 Å and d(O11···HO13) = 1.81 Å. In the **a** the **b** conformations of the C1–C12 system only N3···HO11 bonding is present; relative energies for the most favourable orientation of the O13—H bond: 6.43 (**a**) and 6.28 kcal/mol (**b**); d(N3···HO11) = 1.90 (**a**) and 1.93 Å (**b**).
[e] d(N3···HO11) = 1.90 Å.

predominance of the former (70%). Moreover, the geometry of these forms is strongly influenced by the relative orientation of the O—H bond, the highest destabilization corresponding to an *anti* arrangement of this bond with respect to H-9. In contrast, the ethoxycarbonyl group of the keto ester **7** (Scheme 1) was described by two alternative conformations in which the carbonyl group was eclipsed with C2 and C8, with practically the same contribution.[5,6]

A critical change is found for diols **1** and **2** when the contribution of intramolecular hydrogen bonds is examined (Table 1). The most sterically hindered conformation of the C1—C12 fragment, **a** for **1** and **c** for **2**, becomes the lowest in energy and the participation of the other forms is negligible. Moreover, those forms in which the secondary hydroxy group acts as hydrogen bond donor should amount to about 75% of the equilibrium mixture for a value of the effective dielectric constant $\varepsilon = 1$. On the other hand, the BC conformation of **2** should be additionally stabilized by an intramolecular N···H—O bond. Its formation requires an *anti* orientation of the O11—H bond with respect to H-9 and the participation of this hydroxy group as hydrogen bond donor and acceptor simultaneously. Therefore, the existence of intramolecular hydrogen bonds reduces the molecular mobility mainly in the BC form of **2**, which adopts a pseudo-tetracyclic structure. The ratio of the CC and the BC conformations of **2** is calculated to be around 98:2, considering the most favourable arrangements of the substituents. The most stable forms computed for **1** and **2** are represented in Fig. 1.

Hydrogen bonding exerts a small effect on the

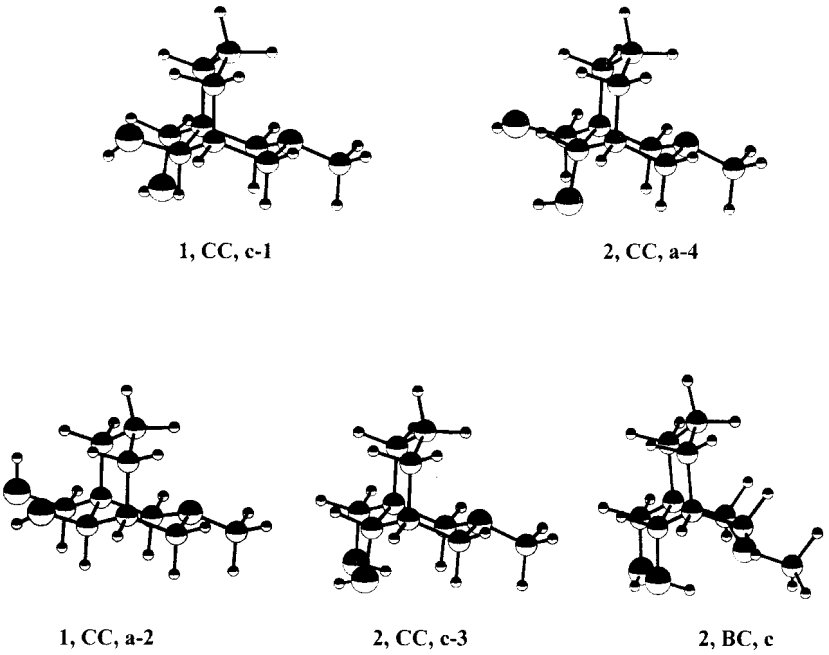


Figure 1. A stereo-view of the sterically more favoured conformations of **1** and **2** (**c-1** and **a-4**, respectively) and those found with the inclusion of intramolecular hydrogen bonding

behaviour of hydroxy esters **3** and **4**. The MM calculations (Table 1) suggest that the energy gained by the intramolecular O—H···N bond is not sufficient to force the piperidine ring into a boat form. Thus, **3** and **4** can be described by a CC form in all conditions. The **a** orientation of the C1—C12 bond of the ethoxycarbonyl group should be additionally stabilized by a weak intramolecular hydrogen bond, increasing the ratio of the **a** and **b** forms from 70:30 to about 90:10.

A hydroxymethyl or ethoxycarbonyl group at the 1-position raises the energy of the BC form for the β epimers **2** and **4** compared with 3-methyl-3-azabicyclo[3.3.1]nonan-9β-ol (**6**) (Scheme 1).[6] According to the MM approach the energy difference between the CC and BC conformations varies from 1.83 (**6**) to 2.35 (**2**) and 5.66 kcal mol^{-1} (**4**) in the most favourable conditions. In any case, the bicyclic system must be predominantly in a slightly flattened CC form and the cyclohexane ring exhibits the greater distortion from the ideal geometry. The same preference was found in the solid state for other bicyclo[3.3.1]nonan-9β-ols substituted at the 1- and 5-positions (x-ray data).[13]

NMR study

Compounds **1**–**4** were studied in depth by ^{1}H and ^{13}C NMR spectroscopy. All bicyclic proton and carbon resonances were assigned by the combined use of 2D-NMR techniques[14] and double resonance experiments. The most relevant data are listed in Table 2.

The C-7 and *N*-CH_3 shifts are in good agreement with the predominance of the CC form, with the *N*-CH_3 group in the equatorial (β) position.[5,6] The comparison of the experimental values of the ^{1}H–^{1}H vicinal coupling constants and those empirically estimated for the computed conformations by using the equation proposed by Haasnoot *et al.*[15] also supports the theoretical predictions. In general, the experimental values are more consistent with those calculated for a CC conformation in which the cyclohexane ring exhibits the greater distortion from the ideal geometry. The most significant deviation is for the value of ^3J(H4β, H5) for **2** in $CDCl_3$ (6.04 Hz), which is larger than that observed for **6** under the same conditions (4.40 Hz), for which a contribution of the BC form of around 15% was proposed.[6] Therefore, for **2** the importance of the BC conformation, stabilized in non-polar solvents by intramolecular O—H···N bonding, could be greater than that estimated by MM calculations (2%). The participation of BC could not be determined by ^{1}H NMR at lower temperatures (203 K in CD_2Cl_2) and a limiting value of around 39% was deduced for **2** in $CDCl_3$ from the model coupling constants calculated for both the CC (3.7 Hz) and BC (9.5 Hz) forms. Although ^3J(H4β, H5) could not be established in DMSO-d_6 or CD_3OD, the decrease in its value on addition of CD_3OD to the $CDCl_3$ solution (4.20 Hz in $CDCl_3$ with 4% CD_3OD) might be related to the reduction of the BC contribution by the solvent effect. The values of ^3J(H4β, H5) confirm that **1**, **3** and **4** adopt a CC conformation. Indeed, these data exclude the contribution of a BC form for the β epimer **4** even in apolar solvents.

Table 2. Selected ^{1}H and ^{13}C data for azabicyclanols **1–4**[a]

	R = CH_2OH						R = CO_2Et	
	1 (9α-OH)			**2** (9β-OH)			**3** (9α-OH)	**4** (9β-OH)
	$CDCl_3$	DMSO-d_6	CD_3OD	$CDCl_3$	DMSO-d_6	CD_3OD	$CDCl_3$	$CDCl_3$
^{1}H δ (ppm)								
H-2β (dd)	1.80	1.89	1.96	2.73	2.22	2.40	2.07	2.63
H-4β (ddd)	2.17	2.07	2.19	2.68	2.47	2.56	2.19	2.56
H-6β (m)	1.89	1.86	1.97	1.52	1.53	1.65	1.99	1.64
H-8β (m)	2.00	1.57	1.75	1.16	1.37	1.41	2.02	1.62
^3J(H,H) (Hz)								
H4α, H5	2.56	2.56	2.75	2.65	—	—	2.56	2.56
H4β, H5	2.56	2.56	2.56	6.04	—	—	2.93	3.66
H5, H6α	2.20	—	—	3.30	—	3.20	—	2.93
H5, H6β	4.40	4.40	4.58	3.58	—	—	4.76	4.03
H6α, H7α	6.23	6.23	6.41	5.49	6.23	6.20	6.23	6.23
H6α, H7β	1.47	—	—	1.47	—	1.50	—	1.47
^{13}C δ (ppm)								
C-7	20.5	20.5	21.7	19.0	20.8	22.0	20.8	20.8
CH$_3$-N	46.0	46.1	46.6	45.9	46.4	46.9	45.8	46.0

[a] Errors: ^{1}H δ ± 0.01 ppm; J ± 0.05 Hz; ^{13}C δ ± 0.1 ppm.

The most relevant information about the conformational preferences of the hydroxymethyl and ethoxycarbonyl groups is derived from the proton chemical shifts. For diols **1** and **2** it was found that H-8β (**1**) and H-2β (**2**) are more deshielded (ca 0.8 ppm) in $CDCl_3$. The value of this effect is around 0.3–0.4 ppm in DMSO-d_6 and CD_3OD, and similar to that observed for H-6β (**1**) and H-4β (**2**) in all the solvents and for H-6(8)β and H-2(4)β in **5** and **6**.[6] These data indicate that the hydroxymethyl group in non-polar solvents adopts a conformation with a 1,3-parallel relative orientation of the two OH groups (Fig. 1), stabilized by intramolecular O···H—O bonding, in which H-8β (**1**) and H-2β (**2**) are deshielded by both OH groups. In dipolar solvents this preference is lacking, in agreement with the flexibility predicted by steric factors.

For hydroxy esters, the similarity of the H-2β and H-4β (**3**) and H-6β and H-8β (**4**) shifts is consistent with the predominance of a conformation in which the carbonyl group of the ethoxycarbonyl moiety is almost eclipsed with the bicyclic carbon C-9, as was discussed above. The ^3J(H9, OH) observed for the α epimer **3** in $CDCl_3$ (1.83 Hz) accounts for a *gauche* orientation of the O—H bond with respect to H-9.[16]

In summary, the combination of the molecular mechanics approach and NMR data provides a satisfactory tool for the study of the conformational properties of the 3-methyl-3-azabicyclo[3.3.1]nonan-9-ol derivatives **1**–**4**. The preferred conformation was found to be a slightly flattened chair-chair (CC) form, with the *N*-CH_3 group in the equatorial position. The diol **2** adopts a CC conformation in CD_3OD and DMSO-d_6, whereas in non-polar solvents ($CDCl_3$) the BC contribution is estimated to be around 39%. The other azabicyclanols exist entirely in the CC form. In the diols **1** and **2** steric factors and hydrogen bonding exert opposite effects on the properties of the hydroxymethyl group. An almost eclipsed arrangement of the carbonyl group and the bicyclic carbon C9 is always preferred for the ethoxycarbonyl moiety in the hydroxy esters **3** and **4**.

EXPERIMENTAL

General. The IR spectra were recorded on a Perkin-Elmer Model 883 spectrophotometer. All NMR spectra [^{1}H, ^{13}C, double resonance (decoupling) experiments, DEPT, COSY-45 and HETCOR] were recorded on a Varian UNITY-300 spectrometer in $CDCl_3$, $(CD_3)_2SO$ and/or CD_3OD at 298 K using standard pulse sequences; ^{1}H NMR spectra of **2** were measured on a Varian UNITY-500 spectrometer; Lorentz–Gauss transformation was used to improve the resolution of the ^{1}H NMR spectra.[14] Yields refer to isolated product.

Synthesis. Compounds **1**–**4** were obtained from ethyl 3-methyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (**7**), prepared as reported earlier.[5] Reduction of **7** with $LiAlH_4$ in dry THF (16 h; 25 °C) followed by hydrolysis and standard work-up gave a mixture of the α (**1**) and β (**2**) epimers of 1-hydroxymethyl-3-methyl-3-azabicyclo[3.3.1]nonan-9-ol (80%; α:β ratio 70:30). Reaction with $NaBH_4$ in dry 2-propanol (24 h; 25 °C) led to a mixture of the α (**3**) and β (**4**) epimers of ethyl 9-hydroxy-3-methyl-3-azabicyclo[3.3.1]nonane-1-carboxylate (60%; α:β ratio 58:42). Silica gel chromatography using dichloromethane–methanol (97:3) (for diols) and hexane–ethyl acetate (85:15) (for hydroxy esters) as eluents

provided **1**, **3** and **4** as pure products and a sample with 91% of **2** (by ^{1}H NMR). The ^{1}H and ^{13}C NMR data are listed in Tables 4 and 5 (supplementary material).

1-Hydroxymethyl-3-methyl-3-azabicyclo[3.3.1]nonan-9α-ol (1). White solid; m.p. 134–136 °C; IR (KBr) 3351 cm^{-1}. Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.81; H, 10.65; N, 7.46%.

1-Hydroxymethyl-3-methyl-3-azabicyclo[3.3.1]nonan-9β-ol (2). White solid; IR (CCl_4) 3351 cm^{-1}. Anal. Found: C, 64.70; H, 10.15; N, 7.78%.

Ethyl 9α-hydroxy-3-methyl-3-azabicyclo[3.3.1]nonane-1-carboxylate (3). Yellow oil; IR (CCl_4) 3516, 1708 cm^{-1}. Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.18; H, 9.53; N, 6.40%.

Ethyl 9β-hydroxy-3-methyl-3-azabicyclo[3.3.1]nonane-1-carboxylate (4). Yellow oil; IR (CCl_4) 3419, 1710 cm^{-1}. Anal. Found: C, 63.75; H, 9.15; N, 6.01%.

Acknowledgements

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